

**CONDITIONAL PETITION FOR EXTENSION OF TIME**

If entry and consideration of the amendments above requires an extension of time, Applicants respectfully request that this be considered a petition therefor. The Commissioner is authorized to charge any fee(s) due in this connection to Deposit Account No. 14-1263.

**ADDITIONAL FEE**

Please charge any insufficiency of fees, or credit any excess, to Deposit Account No. 14-1263.

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**REMARKS**

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments.

Regarding the restriction requirement, Applicants note that the Examiner has made the requirement final. Nevertheless, the basis for the restriction requirement remains unclear. According to the Examiner, "as shown in previous office action, the restriction is based on that different and distinct searches will have to be performed for Groups I and II." However, Groups I and II were both identified as being searched in class 435, subclass 6. Applicants concede that the Examiner also alleged that the search of Group I would not require a search for step (c) of claim 10, and that of Group II would not require a search for step (c) of claim 18. However, Applicants do not understand how this fact, which would be true of any dependent claim, makes, for example, claims 1 and 9 independent and distinct. Rather, the claims all appear to involve closely related subject matter and should be examined together in this one patent application. Therefore, even though the Examiner has made the restriction requirement final, Applicants respectfully request that the Examiner reconsider and withdraw it.

The disclosure was objected to for failing to mention the provisional application and Figures 5A to 5C. In response, Applicants have amended the specification to make the necessary references.

Claim 4 was objected to as ending in a semi-colon. In response, Applicants have amended claim 4 so as to end in a period.

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Claims 1-8 and 16-18 were rejected under 35 USC § 112, second paragraph, as being indefinite. In response, Applicants respectfully submit that the claims are definite.

With respect to the Examiner's points made in numbered paragraph 6 at the bottom of page 3 of the Office Action, Applicants point out that there is no indefiniteness in the use of "selectively randomizing" in the present context. The randomizing is "selective," occurring at selected positions, i.e., at or proximal to the differing site. Accordingly, "selectively randomizing" is accurate and, moreover, definite.

With respect to the Examiner's points made in numbered paragraph 7, Applicants have amended claim 5 in a manner that Applicants believe makes clear what Applicants intend.

With respect to the Examiner's points made in numbered paragraph 8, Applicants refer above to the discussion concerning "selectively randomizing." Applicants respectfully submit that random changes can be introduced at specific sites. In any event, Applicants have amended claim 17 in a manner that, hopefully, will be more palatable for the Examiner.

Finally, with respect to the Examiner's points made in numbered paragraph 9, Applicants have amended claim 18 to provide the necessary antecedent basis.

In view of the foregoing, Applicants respectfully submit that the claims are now definite. An early notice to that effect is earnestly solicited.

That leaves for consideration only the rejection of claims 1-8 and 16-18 under 35 USC § 102(a) or (e) as being anticipated by Patten et al. ("Patten"), US 6,335,160. In response, Applicants would remind the Examiner that anticipation requires that each and every element as set forth in the claim must be found, either expressly or inherently described, in a single prior art

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reference, and, further, the absence in the prior art reference of even a single one of the claim elements is sufficient to negate anticipation. *In re Robertson*, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Patten does not teach “providing at least one polynucleotide having at least one differing site and selectively randomizing the polynucleotides at or in a proximity to the at least one differing site,” as required by the rejected claims, and, therefore, Patten cannot anticipate the rejected claims.

As stated above, the present claims are directed to the “selective randomization” of polypeptides. The term “randomization” in this context is random substitution of the original nucleotides at selected sites. These selected sites, in turn, are those selected sites at which two or more polynucleotides differ from each other in their nucleotide sequence with any other possible nucleotide. As one original nucleotide is replaced with any other nucleotide without predicting or selecting a specific replacement nucleotide, such replacement is random.

As opposed to “DNA shuffling” methods, this randomization entails the substitution of a variety of mutagenic replacement nucleotides that do not necessarily appear in any of the starting genes at these positions (as stated, the starting genes may have an “A” and a “G” at a particular mismatch position, and the claimed invention can target mutagenesis to create clones with “A”, “G”, “C” or “T” at this “selected” position.) In this and other ways, the claimed invention is, thus, distinct from recombination (shuffling) methods. Moreover, in the claimed invention, no sequence related determination is needed to effect either the selection of these sites or their randomization.

In contrast, “randomizing the polynucleotides,” as described by Patten, involves fragmentation that occurs randomly throughout the gene. The fragmentation does not direct randomization of the substitutions at any positions, let alone targeted or selected positions, and, thus, even if, assuming for the sake of argument, it could be considered “random,” it is certainly not “selectively randomizing,” as required by the instant claims. Instead, Patten’s fragmentation generates fragments that are later reassembled to mix and match differing gene segments from the starting genes. It is, thus, a method for “shuffling” the preexisting mutations of the parental genes (see, for example, column 1, lines 45-67, and column 2, lines 25-67, of Patten.) At no point does Patten describe or in any way suggest the randomizing of polynucleotide sequences at sites at which variants differ, but, rather, the random reassembly of fragments of starting genes that carry only the mutations of the parents. Where Patten does describe “random mutagenesis,” it is either site directed using primers, and, thus, requires a previous sequence related determination in order to design and synthesize the “two regions complementary to the DNA” on the oligonucleotides (see, for example, column 3, lines 1-17, of Patten), or is random across the gene and, thus, does not have the component of only randomizing or mutating “specific sites” (see, for example, column 7, lines 23-35, of Patten.) Also, none of the claims of Patten relate to a method of randomization at specific sites with no sequence related determination needed. For example, claim 16 includes only methods of recombination (shuffling), not randomization at “specific sites” and the “segment” that forms the substrates for recombination must be pre-selected using sequence information in order to design and synthesize the described needed nucleotides. Some of Patten’s dependent claims 17-36 include mutagenesis, but using

oligonucleotides with mutations at pre-selected locations and, thus, requiring sequence information, or using random uracil incorporation and, thus, not targeting specific sites, both of which are key aspects of the instantly claimed invention.

In short, nowhere does Patten teach or suggest the claimed invention. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

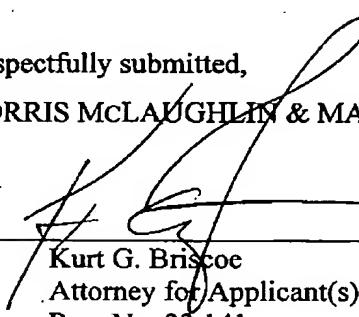
Applicants believe that the foregoing constitutes a bona fide response to all outstanding objections and rejections.

Applicants also believe that this application is in condition for immediate allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

Early and favorable action is earnestly solicited.

Respectfully submitted,  
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